REMARKS

Upon entry of this amendment, claims 57, 59-80, and 82-102 will be pending in the application of which claims 57 and 80 are being amended, and claims 58 and 81 are being canceled.

Claim 57 and 80 are being amended to recite that the particulate microstructures comprise a structural matrix consisting essentially of phospholipid and calcium. The language "consisting essentially of" was previously presented in claim 58, and claim 81, both of which are now being canceled.

This amendment is being made because the Office Action at page 8, first full paragraph, states:

> Applicants arguments filed 8/30/07 have been fully considered but they are not persuasive. Firstly, the examiner points out that the instant claim language, i.e. comprising, does not exclude Hanes' or Unger's polymers. The claims only require phospholipids in the structural matrix, which is clearly taught by both references [Emphasis added.] By amending the claims to include language "consisting essentially of", Applicant is directing the scope of the structural matrix of the particulate microstructures to the specified materials.

Entry of the amendments after final rejection is respectfully requested as they are based on language previously presented in dependent claims and simplify the issues for appeal. No new matter is being added by these amendments.

Rejections Under 35 U.S.C. § 103(a)

I. Claims 57-77 and 80-100 were rejected under 35 U.S.C. § 103(a) as unpatentable over Hanes et al. (US patent no. 5,855,913) in view of Unger (US patent no. 6,120,751) as evidenced by US patent no. 5,776,488, the '488 patent being relied upon only to show the inherent property claimed in claim 72 and 95.

Applicant respectfully traverses the rejection. Independent claims 57 and 80 and the claims dependent therefrom, are patentable under 35 U.S.C. 103(a) over Hanes et al. in view of Unger, because the cited combination does not establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness under 35 U.S.C. 103(a):

(a) The claimed invention must be considered as a whole;

(b) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(c) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(d) Reasonable expectation of success is the standard with which obviousness is determined.

Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

1. <u>The Office Action Does Not Consider the Claimed Invention As a Whole</u>

To establish obviousness, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences <u>themselves</u> would have been obvious, but

whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F. 2d 1530, 218 USPQ 871 (Fed. Cir. 1983).

Neither Hanes et al. nor Unger teach claim 57 or claim 80, taken as a whole, as neither reference teaches an inhaleable powder composition comprising a plurality of particulate microstructures comprising a structural matrix consisting essentially of phospholipid and calcium, an active agent, a mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm^3.

Specifically, Hanes et al. does not teach or suggest an inhalable powder composition comprising particulate microstructures having a structural matrix consisting essentially of phospholipid and calcium. Instead, Hanes et al. teaches:

> The particles may be formed of biodegradable materials such as biodegradable polymers. For example, the particles may be formed of poly(lactic acid) or poly(glycolic acid) or copolymers thereof. Alternatively, the particles may be formed solely of the drug or diagnostic agent and a surfactant. Surfactants can be incorporated on the particle surface for example by coating the particle after particle formation, or by incorporating the surfactant in the material forming the particle prior to formation of the particle.

(Hanes et al., Abstract.) Hanes et al. further teaches that the particles can be made from inorganic and organic materials, such as ceramic or polymer. (Column 5, line 47 to column 6, line 59).

The language in claims 57 and 80 to "a plurality of particulate microstructures comprising a structural matrix consisting essentially of phospholipid and calcium" distinguishes the teachings of Hanes et al. as exemplified above. For example, Hanes et al.'s teachings to forming particles of "biodegradable materials such as biodegradable polymers" do not teach particulate microstructures comprising a structural matrix consisting essentially of phospholipid and calcium. Similarly, Hanes et al.'s teachings that "the particles may be formed of poly(lactic acid) or poly(glycolic acid) or

copolymers thereof" also does not teach or suggest particulate microstructures comprising a structural matrix consisting essentially of phospholipid and calcium. Hanes et al.'s teachings to a ceramic or polymer particle also do not teach particulate microstructures comprising a structural matrix of phospholipid and calcium.

More particularly, Hanes et al.'s teachings that "the particles may be formed solely of the drug or diagnostic agent and a surfactant" teaches away from the claimed particulate microstructures comprising a structural matrix consisting essentially of phospholipid and calcium. The structural matrix consisting essentially of phospholipid and calcium contains calcium. Thus the particulate microstructure is not formed solely of the drug or diagnostic agent and a surfactant, as taught by Hanes et al.

Furthermore, Unger should not be combined with Hanes et al. to derive the claimed particulate microstructures because Unger teaches a different type of particle. Unger teaches particles that have to include a lipid which is covalently bonded to a polymer, and further teaches: "[t]he present invention describes compositions which comprise one or more charged lipids, counter ions and at least one lipid which is covalently bonded to a polymer." (Column 9, line 66 to column 10, line 1). Unger further teaches the importance of the lipid comprising a polymer:

> The lipid covalently bonded to the polymer stabilizes the compositions so that they form well-defined vesicles. If the lipid covalently bonded to the polymer is not used in the compositions of the present invention, the counter ions cause the charged lipids species to form amorphous lipid clumps. In many cases, the lipid clumps may take the form of, for example, condensed lipid bilayers, but the lipid clumps do not form stable vesicles with size distributions suitable, for example, or intravenous injection.

(Column 10, lines 41-49). Thus Unger teaches a particle fabricated using at least one lipid which is covalently bonded to a polymer. Further, Unger teaches that the lipid covalently bonded to the polymer is essential to form a stable vesicle structure.

In contrast, the present claims are to particulate microstructures comprising a structural matrix consisting essentially of a phospholipid and calcium, which is not a lipid covalently bonded to a polymer as taught by Unger. The claimed particulate microstructures are distinguishable because of the "consisting essentially of" language. As explained above, the language "consisting essentially of" means that the structural matrix of the particulate microstructures is directed to the recited materials, and does not include other materials in quantities which would materially affect the basic and novel characteristics of the structural matrix. Thus the claims do not read on the particles described by Unger which include a polymer in a quantity which materially affects the basic and novel characteristics of the structural matrix of the particle.

For these reasons, when claims 57 and 80 are considered as a whole, it is apparent that Hanes et al. and Unger do not teach these claims, because the cited references do not teach a plurality of particulate microstructures comprising a structural matrix consisting essentially of a phospholipid and calcium,

2. Hanes et al. and Unger do not Motivate or Suggest the Desirability of the Claimed Combination.

Under the second part of the obviousness test, the combination of cited references, considered as a whole, must teach or suggest the desirability of the claimed subject matter. To establish a prima facie case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the reference teachings. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). See also MPEP § 2143 - § 2143.03.

As acknowledged by the Examiner, Hanes et al. does not teach the use of calcium in particulate microstructures comprising a structural matrix of phospholipid. In fact, none of the particles taught by Hanes et al. are taught as containing calcium. However, the Office Action relies on Unger to cure the deficiencies of Hanes et al. on grounds that Unger teaches the addition of calcium to particles, and that the Unger

teachings could be combined by one of ordinary skill in the art with the particulate microstructures taught by Hanes et al. to derive the present claims.

Applicant respectfully disagrees. The combination of Hanes et al. and Unger do not motivate or suggest the desirability of the claimed combination to one of ordinary skill in the art. Hanes et al. teaches against addition of other substances, such as calcium, by teaching that the taught particles should be "formed solely of the drug or diagnostic agent and a surfactant". The language "solely" suggests that addition of other components or materials is not desirable in this embodiment. Thus, one of ordinary skill, upon reading Hanes et al. would not be motivated to combine other compounds into the particles taught by Hanes et al. Accordingly, one of ordinary skill in the art would not be inclined to use Unger's teachings to the addition of a different substance, such as calcium, to the particles taught by Hanes et al. as the Hanes et al. particles would then no longer be formed solely of the drug or diagnostic agent and a surfactant, as expressly advocated by Hanes et al.

Furthermore, Unger teaches that calcium added to particles comprising lipid covalently bonded to the polymer, provides unique benefits, namely, "[t]he lipid covalently bonded to a polymer (e.g., DPPE-PEG-5,000) causes compaction of the size of the composition in the presence of a counter ion, such as Ca^{2+}...". Thus, Unger teaches that the lipid covalently bonded to the polymer causes compaction in the size of the composition in the presence of calcium ion. Unger further teaches that:

> Increasing the amount of the lipid covalently bonded to a polymer allows the composition to stabilize at sizes generally under about 1.0 μm in the presence of a counter ion. When the lipid covalently bonded to the polymer is present in an amount less than about 5%, the composition is generally unstable and may precipitate.

(Column 10, lines 61-66.) Thus Unger teaches that the lipid covalently bonded to the polymer is unstable and will precipitate when present in amounts less than 5%. Increasing the amount of lipid provides a stable composition in the presence of the calcium counter ions. Thus Unger teaches that the addition of calcium is needed for

specific type of particle comprising lipid covalently bonded to polymer. Hanes et al. teaches a different type of particle and not particles comprising lipid covalently bonded to polymer. Thus one of ordinary skill in the art would not be motivated to add calcium ions to the Hanes et al. particles, as there would be no apparent benefit to this combination based on the teachings of Unger. Thus the knowledge of the benefits of the claimed particulate compositions must be derived with the benefit of impermissible hindsight vision afforded by the claimed invention.

For these reasons, the combination of Hanes et al. and Unger, when the teachings of these references are considered as a whole, do not motivate or suggest the desirability of the claimed subject matter comprising an inhalable powder composition comprising a plurality of particulate microstructures having a structural matrix consisting essentially of phospholipid and calcium.

3. Particles Resulting from the Combination of Hanes et al. and Unger would not Necessarily have a Reasonable Expectation of Success.

Furthermore, the particles that result from the combination of Hanes et al. and Unger would not necessarily have a reasonable expectation of success based on the teachings of Hanes et al. and Unger. Hanes et al. teaches that the particles should be "formed solely of the drug or diagnostic agent and a surfactant". Thus Hanes et al. teaches against addition of other substances, such as calcium, to the particles. Consequently, upon reading Hanes et al., one of ordinary skill would not have a reasonable expectation of success in the fabrication of particles in which compounds other than the drug or diagnostic agent and surfactant taught by Hanes et al. were incorporated into the particles.

Further, Unger teaches that calcium is needed to be added to particles comprising lipid covalently bonded to the polymer. Unger further teaches that the lipid covalently bonded to the polymer causes compaction in the size of the composition in the presence of calcium ion. Unger also teaches that when the lipid covalently bonded to the

polymer is present in an amount less than about 5%, the composition is generally unstable and may precipitate; however, the lipid covalently bonded to a polymer can be stabilized in the presence of a counter ion. Thus Unger teaches the addition of calcium is necessary for stabilizing a specific type of particle comprising lipid covalently bonded to polymer. Hanes et al. does not teach such particles. Instead Hanes et al.'s teachings are directed to other types of particles, such as polymer, ceramic, or surfactant based particles. Thus one of ordinary skill in the art would not be motivated to add calcium ions to the Hanes et al. particles, as there would be no reason that this proposed combination would have a reasonable expectation of success based on the teachings of Unger or Hanes et al.

Furthermore, Unger et al. teaches that the addition of calcium can result in particulate aggregation. Specifically Unger teaches:

> ... the counter ions (calcium) form salt bridges which crosslink the charged lipids to form aggregates **or** multilamellar vesicles. The aggregates **or** multilamellar vesicles may be referred to cochleates, which may be in the form of a tubule or a spiral. [Emphasis added.] (Unger, Column 10.)

Unger further teaches:

> Studies have described the effects of calcium and other multivalent cations on membrane asymmetry, lipid distribution, vesicle size, aggregation and fusion. Although the underlying physical causes for the phenomena are debatable, general consensus exists that multivalent cations, such as calcium and magnesium, in the external environment of phospholipid vesicles cause the structures to **aggregate** into larger, multilamellar structures and promotes fusion. ...
>
> ... The effects of calcium-induced aggregation are so pronounced that efforts have been undertaken to limit the effect in order to control the size of liposomes used in drug delivery systems by forming vesicles in which calcium ions are confined to outer surfaces of the bilayer. ...

[Emphasis added]. (Unger, column 1, line 50 to column 2, line 9.)

Thus Unger teaches that the counter ions form bridging structures that form

aggregates or multilamellar vesicles. Unger also teaches "[a] vesicle refers to an entity which is generally characterized by the presence of one or more walls or membranes which form one or more internal voids." (Column 4, lines 18-21). Thus the vesicles taught by Unger are enclosed structures with internal volumes, and Unger further teaches that these vesicle structures form multilamellar vesicles with calcium addition.

Both particle aggregation and multilamellar structures, as taught by Unger to result from the addition of calcium to lipids covalently bonded to polymers, are undesirable. Aggregated particles are undesirable for inhalable compositions because such particles would become larger and as a result would not penetrate deep into the lungs as desired for many inhalation therapies. Multilamellar structures may also be undesirable as the thick or multiple layered structures may be more difficult to assimilate in the lungs. Thus both structures teach away from the claimed inhaleable powder composition comprising a plurality of discrete particulate microstructures which exhibit reduced aggregation. Thus Unger's teachings do not motivate addition of calcium to the particulate structures taught by Hanes et al. to form discrete, non-aggregated structures, but instead teach that aggregation and multilayer wall structures, result from the addition of calcium to lipid covalently bonded to polymer.

The present application expressly teaches the undesirability of forming aggregates of particulate microstructures:

> In order to maximize dispersibility, dispersion stability and optimize distribution upon administration, the mean geometric particle size of the perforated microstructures is preferably about 0.5-50 μm, more preferably 1-30 μm. It will be appreciated that large particles (i.e. greater than 50 μm) may not be preferred in applications where a valve or small orifice is employed, since large particles tend to aggregate or separate from a suspension which could potentially clog the device.

(Specification, page 32, lines 11-16.)

> With respect to the advantageous deposition profile provided by the instant invention it is well known that MDI propellants typically force suspended particles

> out of the device at a high velocity towards the back of the throat. Since prior art formulations typically contain a significant percentage of large particles and/or aggregates, as much as two-thirds or more of the emitted dose may impact the throat.

(Specification, page 39, lines 24-28.) Thus, the Specification teaches that aggregated particles are undesirable because they tend to separate from a suspension and clog the inhaler device. Also, as explained, prior art formulations such as those taught by Unger contain aggregates which result in as much as two-thirds or more of the emitted dose impacting the throat and not traveling deep into the lungs, which is undesirable in inhalation therapy.

It should be further noted that Unger also does not teach particulate microstructures having the aerodynamic properties of the claimed particulate microstructures. Specifically, Unger does not teach particles suitable for an inhalable composition, and which have a mean aerodynamic diameter of less than 5 microns, a mean geometric diameter of 1-30 microns, and a bulk density of less than about 0.5 g/cm^3. This may well be because the Unger particles, as explained above, do not possess the claimed aerodynamic qualities because they are aggregated or have excessively thick multilamellar wall structures. Thus the teachings of Unger do not suggest combination with Hanes et al. and even if such a combination were performed, there is no indication in the references that it would have a reasonable expectation of success.

Further, Hanes et al. teaches that an organic solvent dissolved polymer is suspended in an aqueous medium containing a surface active agent, such as PVA, to form an emulsion that is stirred until the organic solvent evaporates to leave behind polymer particles. If the particles made by this method were further aggregated with the addition of calcium to the aqueous medium as taught by Unger, the resultant composition would have large aggregated particles with particle sizes larger than those described by Hanes et al.. In fact, Hanes et al. teaches the use of surfactants to reduce particle agglomeration, which further evidences that Hanes et al. teaches against the use of a calcium aggregating agent as taught by Unger, and evidences the lack of motivation for

this combination of references.

For these reasons, the combination of Hanes et al. and Unger, when considered as a whole, do not teach or suggest the desirability of the claimed inhalable powder composition comprising a plurality of particulate microstructures having a structural matrix consisting essentially of phospholipid and calcium, as in claims 57 and 80. Hanes et al. does not teach particles containing calcium. Unger et al. teaches addition of calcium to the lipid covalently bonded to a polymer, and not a particulate microstructure comprising a structural matrix of phospholipid. Unger also teaches that calcium addition results in the aggregation of vesicles or multilamellar vesicles, which are both undesirable. Further, the reasons for which Unger motivates application of calcium to a composition comprising a lipid covalently bonded to a polymer, do not apply to the particles of Hanes et al. as they are not "lipid covalently bonded to a polymer". Unger further does not teach aerodynamic particles. Thus claims 57 and 80 and their dependent claims are not rendered unpatentable by Hanes et al. in view of Unger. Accordingly, the Examiner is respectfully requested to reconsider the present rejection, and allow the pending claims.

II. Claims 78 and 101 were rejected under 35 U.S.C. § 103(a) as unpatentable over Hanes et al. in view of Unger and further view of Igarashi (US patent no. (4,201,774).

Claims 78 and 101 are to an inhalable powder composition in which the bioactive agent is an aminoglycoside antibiotic.

As acknowledged by the Examiner, Hanes et al. does not teach an aminoglycoside antibiotic. Further neither Hanes et al. nor Unger teach an inhalation powder composition comprising particulate microstructures comprising a structural matrix consisting essentially of phospholipid and calcium, as recited in parent claims 57 and 80. Instead, Hanes et al. teaches polymer or ceramic particles, or that the particles should be formed solely of the drug or diagnostic agent and surfactant. Hanes does not teach an

inhalable composition comprising particulate microstructures containing calcium. Unger teaches particles that include a lipid covalently bonded to a polymer. Further, Unger et al. teaches addition of calcium to lipid covalently bonded to a polymer, and thus, only motivates application of calcium to a composition comprising a lipid covalently bonded to a polymer and not the Hanes et al. particles. Unger also does not teach aerodynamic particles or their desirable properties. Thus neither reference teaches or suggests, or motivates derivation of an aerodynamic particle comprising a structural matrix consisting essentially of phospholipid and calcium, as claimed.

Igarashi et al. does not make up for the deficiencies of Hanes et al. or Unger as Igarashi et al. also does not teach or suggest particulate microstructures comprising a structural matrix consisting essentially of phospholipid and calcium, as claimed. Thus Hanes et al., Unger and Igarashi, do teach or suggest the powder composition recited in claims 57 and 80.

Furthermore, Hanes et al., Unger or Igarashi do not teach or suggest that it is desirable to include a phospholipid having a gel to liquid crystal transition temperature of greater than 40°C, as claimed in claim 80. Nor is this teaching to a phospholipid having a desirable gel-to-liquid transition temperature range obvious to one of ordinary skill, simply from a teaching that phospholipids are desirable to form particulate microstructures.

For these reasons, Applicant respectfully submits that claims 78 and 101, which depend on claims 57 and 80, are allowable over the cited references.

III. Claims 79 and 102 were rejected under 35 U.S.C. § 103(a) as unpatentable over Hanes et al in view of Unger and in further view of Benson et al. (US patent no.5,006,343).

Claims 79 and 102, are to an inhaleable powder composition that includes a bioactive agent that is a fungicide.

Claims 79 and 102 are patentable over the cited references because Hanes et al., in view of Unger, and further in view of Benson et al., do not teach or suggest parent independent claims 57 and 80. Hanes et al. does not teach an inhalable composition comprising a plurality of particulate microstructures comprising a structural matrix consisting essentially of phospholipid and calcium. The Office Action also acknowledges than Hanes et al. does not teach the specific use of fungicides, or particles comprising calcium. Unger et al. teaches addition of calcium to the lipid covalently bonded to a polymer, and thus, does not motivate application of calcium to the Hanes et al. particles. Unger also does not teach aerodynamic particles as claimed.

Benson also does not teach or suggest an inhaleable composition comprising a plurality of particulate microstructures comprising a structural matrix consisting essentially of phospholipid and calcium. The Office Action cites Benson only for teaching a fungicide. Thus, Hanes et al., Unger and Benson do not teach or suggest a powder composition as claimed in claims 57 or 80.

Furthermore, Hanes et al., Unger and Benson do not teach or the desirability of particulate microstructures that include phospholipid having a gel to liquid crystal transition temperature of greater than 40°C, as claimed in claim 80. Nor is this teaching to a particular temperature range obvious to one of ordinary skill, simply from a teaching that phospholipids are desirable to form particulate microstructures.

For these reasons, the Examiner is respectfully requested to allow claims 79 and 102, which depend on claims 57 and 80, over the cited references.

IV. Claims 57-77 and 80-100 were rejected under 35 U.S.C. § 103(a) as unpatentable over Hanes et al in view of Mathiowitz et al. (US patent no. 6,248,720) or Cohen et al. (US patent no. 5,149,543), respectively as evidenced by US patent no. 5,776,448 - which is being relied on only to show the inherent property claimed in claims 72 and 95.

The combination of Hanes et al. and Mathiowitz et al. or Cohen et al. do not teach claim 57 or claim 80, when these references are taken as a whole, as none of the references teach or suggest an inhalable powder composition comprising particulate microstructures made of a structural matrix consisting essentially of phospholipid and calcium.

Hanes et al. teaches that particles may be formed of biodegradable materials such as biodegradable polymers such as poly(lactic acid) or poly(glycolic acid) or copolymers thereof; solely of the drug or diagnostic agent and a surfactant; or ceramics or polymers. (Abstract, Column 5, line 47 to column 6, line 59). The language in claims 57 and 80 to "a plurality of particulate microstructures comprising a structural matrix consisting essentially of phospholipid and calcium" distinguishes the teachings of Hanes et al.. For example, Hanes et al.'s teachings that "the particles may be formed solely of the drug or diagnostic agent and a surfactant" is also not the same as the claimed structural matrix consisting essentially of phospholipid and calcium, because the claimed structure contains calcium.

The Office Action relies upon Mathiowitz et al. or Cohen et al., to cure the deficiencies of Hanes et al. with regard to the teaching of calcium in the structural matrix.

However, Mathiowitz et al. should not be combined with Hanes et al. to derive the claimed particulate microstructures because Mathiowitz et al. also teaches a different type of particle. Mathiowitz et al. teaches a method for gene therapy using nucleic acid loaded polymeric microparticles. Mathiowitz et al. further teaches that "[t]he microparticle preferably is bioadhesive." (Column 4, lines 18-20).

Mathiowitz et al. also teaches:

> As will be seen from the examples below, a variety of polymers have been tested in the methods of the invention, including polyesters such as poly(lactic acid), poly(lactide-co-glycolide) in molar ratios of 50:50 and 75:25; polycaprolactone; polyanhydrides such as poly(fumaric-co-sabacic) acid or P(FA:SA) in molar ratios of 20:80 and 50:50; poly(carboxyphenoxypropane-co-sebacic) acid or P(CPP:SA) in molar ratio of 20:80; and polystyrenes or PS.

(Column 7, lines 44-51). However, none of the polymer tested by Mathiowitz et al. is a phospholipid as claimed. Mathiowitz et al. further lists a large number of polymers at col. 11, line 5 to col.13, line 3, which can be used to allegedly prepare the described particles. However, even in this extensive list of polymers, Mathiowitz et al. does not mention a single phospholipid.

Thus, Mathiowitz et al. simply does not teach the same type of particle as that which is being claimed. Applicant is not claiming ANY microparticle. Applicant is claiming a particular microstructure comprising a structural matrix consisting essentially of phospholipid and calcium. A polymer microparticle as taught by Mathiowitz et al. is a different type of particle; and consequently, the teachings of Mathiowitz et al., relating to the addition of calcium to the polymer microparticle would simply not be applied to the particles taught by Hanes et al. to derive the claimed microparticle which contains a structural matrix of phospholipid.

In fact, Mathiowitz et al. teachings provide support for Applicants position because Mathiowitz et al. expressly teaches incorporating an insoluble metal compound to achieve a particular result. Specifically, Mathiowitz et al. teaches:

> The bioadhesive properties of a polymer are enhanced by incorporating a metal compound into the polymer to enhance the ability of the polymer to adhere to a tissue surface such as mucosal membrane. Metal compounds which enhance the bioadhesive properties of a polymer preferably are water-insoluble metal compounds, such as water-insoluble metal oxides and hydroxides. The metal compounds can be incorporated within a wide range of hydrophilic and hydrophobic

> polymers including proteins, polysaccharides and synthetic biocompatible polymers. As defined herein, a water-insoluble metal compound is defined as a metal compound with little or no solubility in water, for example, less than about 0.0-0.9 mg/ml.

(Col. 13, lines 22-34.) Mathiowitz et al.'s teachings to use of an insoluble metal compound to enhance the bioadhesive properties of a polymer particle have little to do with Applicant's claimed particulate microstructure comprising a structural matrix consisting essentially of phospholipid and calcium, or the particles taught by Hanes et al.

Thus, Mathiowitz et al. should not be combined with Hanes et al. because Mathiowitz et al. teaches at different type of particle, namely in polymeric particle, which is preferably made of a bioadhesive polymer, and further teaches a different reason for the addition of a different compound, namely an insoluble metal compound to this different particle. Furthermore, the particles that would result from the combination of Hanes et al. and Mathiowitz et al. would not necessarily have a reasonable expectation of success based on the teachings of Hanes et al. and Mathiowitz et al., and without the knowledge derived from Applicants invention.

The Office Action alternatively relies on Cohen et al. to cure the deficiencies of Hanes et al. However, Cohen et al. also does not cure the deficiencies of Hanes et al., because Cohen et al. also teaches different particles, namely ionically cross-linked polymeric microcapsules. Cohen et al. further teaches that the water-insoluble polymer with charged side chains are crosslinked with the multivalent ions of the opposite charge to form a gel encapsulating biological material. (Abstract.) Cohen et al., further teaches a large number of water-insoluble polymers at column 3, line 62 to column 4, line 19. However, Cohen et al. does not mention phospholipid as a polymer which can be used to form the ionically cross-linked polymeric microcapsules. Thus, the teachings of Hanes et al. and Cohen et al. cannot be used to derive the present claimed particulate microstructures.

Further, while Cohen et al. teaches that calcium ions can be used to cross-link the recited water-insoluble polyelectrolyte polymers, Cohen et al. does not teach or suggest that calcium should be used with a phospholipid to form the structural matrix of a particulate microstructure. Thus Cohen et al.'s teachings to ionically cross-linking polyelectrolyte polymers with metal ions, and Hanes et al's teachings to a different type of particle, do not motivate combination of these references to derive of Applicant's claimed particulate microstructure comprising a structural matrix consisting essentially of phospholipid and calcium. Furthermore, the particles that would result from the combination of Hanes et al. and Cohen et al. would not necessarily have a reasonable expectation of success, based on the teachings of Hanes et al. and Cohen et al., and without the knowledge derived from Applicants invention.

For these reasons, Hanes et al., Mathiowitz et al., and Cohen et al. do not teach claims 57 and 80 to an inhalable powder composition comprising a plurality of particulate structures which have a structural matrix consisting essentially of phospholipid and calcium.

IV. Claims 57-77 and 80-100 were rejected under 35 U.S.C. § 103(a) as unpatentable over Hanes et al in view of Papahadjopoulos at al. (Cochleate lipid cylinders: Formation by fusion of unilamellar lipid vesicles, Biochimica et Biphysics, 394 (1975), 43-491) as evidenced by US patent no. 5,776,448 - which is being relied on only to show the inherent property claimed in claims 72 and 95.

The combination of Hanes et al. and Papahadjopoulos et al. also does not teach claim 57 or claim 80, when taken as a whole, as these references do not teach or suggest an inhalable powder composition comprising particulate microstructures made of a structural matrix consisting essentially of phospholipid and calcium.

Hanes et al. teaches that particles may be formed of biodegradable materials such as biodegradable polymers such as poly(lactic acid) or poly(glycolic acid) or copolymers thereof; solely of the drug or diagnostic agent and a surfactant; or ceramics or

polymers. Claims 57 and 80 recite, inter alia, "a plurality of particulate microstructures comprising a structural matrix consisting essentially of phospholipid and calcium." The present claims can be distinguished from the teachings of Hanes et al. because Hanes et al. teaches that "the particles may be formed solely of the drug or diagnostic agent and a surfactant". Hanes et al.'s teachings are not to particulate microstructures having a structural matrix consisting essentially of phospholipid and calcium, because the claimed structure contains calcium, whereas Hanes et al. teaches against additions of other materials to the surfactant particle.

Further, as acknowledged by the Office Action, Hanes et al. does not teach the use of calcium in the structural matrix.

The Office Action relies upon Papahadjopoulos et al. to cure the deficiencies of Hanes et al. with regard to the lack of teaching of calcium in the structural matrix. However, Papahadjopoulos et al. should not be combined with Hanes et al. to derive the claimed particulate microstructures because Papahadjopoulos et al. does not teach aerodynamic particles for inhalation. Papahadjopoulos et al.'s teachings are directed to forming cochleate lipid cylinders by fusion of unilamellar lipid vesicles. Specifically, Papahadjopoulos et al. teaches:

> We propose that fusion of unilamellar phosphatidylserine vesicles in the presence of Ca^{2+} creates large planar lamellae which roll up to form cylinders. We suggest the term cochleate cylinders [Greek for snail with spiral shell] for the structures, which appeared to be formed from spirally folded lipid bilayers. Incubation of cochleate cylinders with Ca^{2+} -chelating agents results in a further structural transformation to create very large closed unilamellar vesicles. These findings therefore suggest a potential new method for creating very large unilamellar vesicles suitable for studies of the properties of lipid bilayers [5] and the interaction of unilamellar vesicles with cultured cells [6, 7, 8].

(page 484, lines 3-11.) Thus Papahadjopoulos et al. teaches creating very large unilamellar vesicles suitable for studies of the properties of lipid bilayers.

Thus Papahadjopoulos et al. does not teach the claimed inhalable composition comprising a plurality of particulate microstructures having an mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm^3. Further, there is no indication in the teachings of Papahadjopoulos et al. that the large unilamellar vesicles would be inhalable as Papahadjopoulos et al. does not teach particles having a mean aerodynamic diameter of less than 5 microns. Thus, the Office Action is clearly not considering the teachings of Papahadjopoulos et al. as a whole.

Further, one of ordinary skill in the art, upon reading Hanes et al. and Papahadjopoulos et al. would not be motivated to derive the claimed inhalable powder composition. Hanes et al. teaches that it is not desirable to add materials to a particle formed of a surfactant. Papahadjopoulos et al.'s teachings are directed to forming very large unilamellar vesicles suitable for studies of the properties of lipid bilayers, and not an inhaleable powder composition. This one of ordinary skill in the art would not be motivated to combine the teachings of Hanes et al. and Papahadjopoulos et al. to derive the present claims. It is not clear from the Office Action's arguments why one of ordinary skill in the art would combine a reference teaching large unilamellar vesicles with another teaching inhaleable particles, which are both completely different particles, to derive an inhaleable powder composition as claimed. In fact the teachings of Papahadjopoulos et al. to the formation of large particles would suggest the opposite, namely that inhaleable particles cannot be formed using the teachings of Papahadjopoulos et al.

Further, even if one of ordinary skill in the art did perform such an unjustifiable combination, there is no reasonable expectation of success that the large unilamellar vesicles as taught by Papahadjopoulos et al. can be made to be the claimed particulate microstructures have an mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm^3.

For these reasons, the combined teachings of Hanes et al. and Papahadjopoulos et al. do not render obvious claims 57 and 80 or the claims dependent therefrom.

V. Claims 78 and 101 were rejected under 35 U.S.C. § 103(a) as unpatentable over Hanes et al. in view of Mathiowitz et al. or Cohen et al. or Papahadjopoulos et al.

Claims 78 and 101 are to an inhalable powder composition in which the bioactive agent is an aminoglycoside antibiotic.

The combination of Hanes et al. and Mathiowitz et al. or Cohen et al. or Papahadjopoulos et al. do not teach claim 57 or claim 80, when these references are taken as a whole, as none of the references teach or suggest an inhalable powder composition comprising particulate microstructures made of a structural matrix consisting essentially of phospholipid and calcium, and the particulate microstructures having an mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm^3, as recited in parent claims 57 and 80.

Hanes et al. teaches that particles may be formed of biodegradable materials such as biodegradable polymers such as poly(lactic acid) or poly(glycolic acid) or copolymers thereof; solely of the drug or diagnostic agent and a surfactant; or ceramics or polymers. (Abstract, Column 5, line 47 to column 6, line 59). The language in claims 57 and 80 to "a plurality of particulate microstructures comprising a structural matrix consisting essentially of phospholipid and calcium" distinguishes the teachings of Hanes et al. For example, Hanes et al.'s teachings that "the particles may be formed solely of the drug or diagnostic agent and a surfactant" is also not the same as the claimed structural matrix consisting essentially of phospholipid and calcium, because the claimed structure contains calcium.

As acknowledged by the Office Action, Hanes et al. does not teach the use of calcium in the structural matrix. The Office Action relies upon Mathiowitz et al. or Cohen et al. or Papahadjopoulos et al., to cure the deficiencies of Hanes et al. with regard to the teaching of calcium in the structural matrix.

However, Mathiowitz et al. should not be combined with Hanes et al. to derive the claimed particulate microstructures because Mathiowitz et al. also teaches a different type of particle comprising polymeric microparticles. Mathiowitz et al. also teaches that "[t]he microparticle preferably is bioadhesive." Mathiowitz et al. further lists a large number of polymers which can be used to prepare the described particles at col. 11, line 5 to col.13, line 3. However, even in this extensive list of polymers, Mathiowitz et al. does not mention a single phospholipid. Thus Mathiowitz et al. simply does not teach the same type of particle as that which is being claimed. Further, Mathiowitz et al.'s teachings to use of an insoluble metal compound to enhance the bioadhesive properties of a polymer particle have little to do with Applicant's claimed inhaleable composition comprising particulate microstructures comprising a structural matrix consisting essentially of phospholipid and calcium. Thus Mathiowitz et al. should not be combined with Hanes et al..

Cohen et al. does not cure the deficiencies of Hanes et al. because Cohen et al. also teaches different particles, namely ionically cross-linked polymeric microcapsules. Cohen et al. further teaches that water-insoluble polymer with charged side chains can be crosslinked with the multivalent ions of the opposite charge to form a gel encapsulating biological material. As with Mathiowitz et al., Cohen et al. does not teach a particulate microstructure comprising a structural matrix consisting essentially of phospholipid and calcium. Cohen et al. does not mention phospholipid as a polymer which can be used to form the ionically cross-linked polymeric microcapsules. Further, Cohen et al. teaches that calcium ions can be used to cross-link the recited water-insoluble polyelectrolyte polymers. Nowhere, however, does Cohen et al. teach or suggest that calcium and should be used with a phospholipid to form the structural matrix of a particulate microstructure as claimed. Thus, the teachings of Hanes et al. and Cohen

et al. cannot be used to derive the present claimed particulate microstructures.

Papahadjopoulos et al. also does not cure the deficiencies of Hanes et al. because Papahadjopoulos et al. does not teach the claimed inhalable composition comprising a plurality of particulate microstructures having an mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm^3. There is no indication in the teachings of Papahadjopoulos et al. that the taught large unilamellar vesicles would be suitable as inhalable particles or have a particular aerodynamic diameter. Further, one of ordinary skill in the art, would have no motivation to combine Papahadjopoulos et al.'s teachings to forming large unilamellar vesicles with Hanes et al's teachings to forming inhaleable powders, to derive an inhaleable powder composition as claimed. In fact the teachings of Papahadjopoulos et al. to the formation of large particles would suggest the opposite, namely that aerodynamic particles cannot be formed. Further,, there is no reasonable expectation of success that the large unilamellar vesicles as taught by Papahadjopoulos et al. can be made to be the claimed particulate microstructures have an mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm^3. For these reasons, the combined teachings of Hanes et al. and Papahadjopoulos et al. do not render claims 57 and 80, obvious.

For these reasons, Hanes et al. and Mathiowitz et al. or Cohen et al. or Papahadjopoulos et al. do not teach claims 57 and 80, or claims 78 and 101 which are dependent therefrom.

VI. Claims 79 and 102 were rejected under 35 U.S.C. § 103(a) as unpatentable over Hanes et al. in view of Mathiowitz et al. or Cohen et al. or Papahadjopoulos et al.

Claims 79 and 102, are to an inhaleable powder composition that includes a bioactive agent that is a fungicide.

The combination of Hanes et al. and Mathiowitz et al. or Cohen et al. or Papahadjopoulos et al. do not teach claim 79 or 102, when these references are taken as a whole, as none of the references teach or suggest an inhalable powder composition comprising particulate microstructures made of a structural matrix consisting essentially of phospholipid and calcium, and the particulate microstructures having an mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm^3, as recited in parent claims 57 and 80. The arguments for the same are provided above and to avoid repetition will not be repeated herein.

For these reasons, Hanes et al. and Mathiowitz et al. or Cohen et al. or Papahadjopoulos et al. do not teach claims 57 and 80, or claims 78 and 101 which are dependent therefrom.

VII. Provisional Double Patenting Rejections

The provisional double patenting rejections are being addressed by the filing of Terminal Disclaimers.

For the foregoing reasons, allowance of the instant application is respectfully requested. Should the Examiner have any questions regarding the above amendments or remarks, the Examiner is requested to telephone Applicant's representative at the number listed below.

Respectfully submitted,

JANAH & ASSOCIATES, P.C.

Date: January 9, 2008

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